PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

29/16

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/046477	International filing date *(day/month/year)* 21.12.2005
Priority date *(day/month/year)* 21.12.2004	
International Patent Classification (IPC) or both national classification and IPC INV. C07D471/04 A61K31/437 A61P31/12	
Applicant GILEAD SCIENCES, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Stroeter, T Telephone No. +49 89 2399-8088

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 3,4

because:

☒ the said international application, or the said claims Nos. 3,4 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. -

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/046477

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1,2,5
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3 and 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The present application is directed to a compound which is useful in the treatment of viral infections including hepatitis C virus.

2 Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004

D2: WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005

Concerning document D2 please see item VI.

3 The presently claimed compound differs from the structurally closest prior art compounds revealed in D1 which are also antiviral compounds through the phenyloxazolyl group instead of a phenyl or pyridyl group. This structural modification starting from the compounds of D1 in order to solve the problem of providing an alternative antiviral compound useful in the treatment of HCV is not obvious and thus, compound claim 1 and consequently further claims 2-5 appear to be novel (Article 33(2) PCT) and inventive (Article 33(3) PCT).

However, it is remarked that the findings on inventive step are made on condition that experimental data can be provided at a later stage to support that the claimed compound indeed shows the alleged pharmacological effect and as such solves the

problem posed.

4 The subject-matter of the present claims 1, 2 and 5 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claims 3 and 4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

The International Search Report mentions P-document D2 which does not form part of the state of the art according to Rule 64.1(b) PCT. For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid. The Applicant is informed, that D2 discloses the compound of example 6 and related subject-matter which is novelty-destroying for present claim 1-5.

Re Item VII
Certain defects in the international application

When entering the regional phase at the EPO, the expression "incorporated by reference" is to be deleted wherever it may appear in the present description.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

30/3

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2005/026606	International filing date *(day/month/year)* 26.10.2005
Priority date *(day/month/year)* 27.07.2004	
International Patent Classification (IPC) or both national classification and IPC C07D473/00, C07D471/04, C07D519/00, A61K31/52	
Applicant GILEAD SCIENCES, INC.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Frelon, D

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/026606

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 71-78

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 71-78 with regards to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/026606

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-55,60,62-78
	No:	Claims	56-59,61
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-78
Industrial applicability (IA)	Yes:	Claims	1-70
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item I
Basis of the report

The present claims 1-63,70-78 relate to an extremely large number of possible compounds (claims 64-69 concern the specific examples of the illustrations). In addition, it is noted that unspecific and/or open expressions like aryl, heterocycle, aminoacid residue, ring, linking group, isomers add to the unclarity of the claims. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed (see examples 1-6 on pages 117-121).
The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims (PCT Guidelines 9.19 and 9.23).

The search was necessarily restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae, as described in formulae (A1) (fourth aspect, page 27) and (B) (twelth aspect, page 47) considering furthermore in the case of the later formula that R^{25} and R^{26} should be absent for reason of consistency with the support of the examples and with the valence of the nitrogen atoms (the present drawing is misleading); in other words, the searched compounds are the ones wherein Y-R^1 and R^3 = a (hetero)ring, X = alk, O-alk, S-alk, N-alk and R^{25}, R^{26} are absent.

Re Item II

The intermediate document D10 is relevant for the purposes of Rules 33.1c, 64.3 and 70.10 PCT (see section VI, certain documents), but since the priority documents are not available at the time of establishing the written opinion, they are not taken into account. It is based on the assumption that all claims enjoy priority rights from the filing date of the priority document(s). If it later turns out that this assumption is not correct, the intermediate document in the International Search Report (ISR) could become relevant in order to assess whether the claims satisfy the criteria set forth in Art. 33(1) PCT.
If the priority date is not valid for the complete claimed subject-matter, this document may become relevant prior art in a possible regional/national phase.

Re Item III

Claims 71-78 are directed to methods for treatment of the human or animal body by surgery or therapy and/or to diagnostic methods practised on the human or animal body. They relate to subject-matter considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claims 71-78 on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

See ISR.

2. Novelty - Unity

2.1 Despite the scope limitations necessary to proceed for a meaningfull International

search, D1 and D2 disclose compounds which are novelty detroying against compounds of formula (B), *i.e.* imidazopyridine derivatives (claims 56-59 and 61). Note that D10 discloses also compounds which fall in the searched domain. The known compounds are also described as antiviral agents.

In the frame of the limited searched scope, compounds of formula (A) appear to be novel. These novel compounds, *i.e.* imidazopyrimidine derivatives (U = N), are characterized by their substitution pattern such that Y-R^1 and R^3 represent a ring.

2.2 Due to the fact that compounds of formula (B) are known, the common concept they share with the compounds of formula (A) is known and cannot be identified as a *same or corresponding special technical feature* that clearly defines a common contribution over the art. This means that the technical relationship linking the subject-matters claimed *per se* in claims 1 and 56 which can be individualized in the sense of Rule 13.2 PCT lacks to form a (common) *single general inventive concept* in the sense of Rule 13(1) PCT, *i.e.* to establish the unity of invention.

These considerations indicate that the present application is not unitary. It appears therefore that at least two inventions are covered by the present application:
- a first invention A represented by compounds of formula (A)
- a second invention B represented by compounds of formula (B) (this last invention should be reformulated to disclaim the known compounds).

The Applicant's attention is drawn to the fact that the requirements of unity is not met when a significant structural and/or functional element shared by all the claimed alternatives lacks to qualify a required "same or corresponding special technical feature" (Rule 13.2 PCT) that clearly defines the very invention as a contribution over the art.

3. Inventive step

3.1 The problem underlying the present application is to provide antiviral compounds. The compounds of the prior art D1 can be considered as the closest prior art.

Invention A

3.2 The difference of the subject-matter of invention A and the one of D1 is essentially to be seen in the condensed system wherein the ring carbon atom of the 7-position of the imidazopyridine is replaced by a nitrogen atom to form the imidazopyrimidine of invention A. Such an exchange belongs to the general knowledge of bioisosterism of C and N as ring members commonly used in drug design studies. Document D3 illustrates also this common knownledge.

In order to demonstrate the presence of an inventive step for the novel compounds, it must be clearly apparent that the differentiating feature is responsible for an unexpected effect. If this demonstration should be made by means of comparative tests, the compounds to be compare should be chosen such that they only differ by the diffentiating feature.

Invention B

3.3 The compounds of formula (B) appear to be selected from D1. The present application does not disclose any characteristic feature which would help to identify the selection and render this selection novel. As such, compounds of formula (B) are not inventive as they are expected to be active as antiviral. However, if the selection could be specifically identified, it should be shown that the distinguishing feature for the selection is responsible for a surprising effect.

3.4 The Applicant's attention is drawn to the fact that the claims as presently drafted do not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth for the claimed scope.

Further remarks

3.4.1 It is realized that the Applicant is entitled to claim all **obvious** modifications of what was concretely described and that alternative variations have to be supported by the description, *i.e.* a certain number of examples.

Open and non limitative (generalizing) expressions or terms like "*aryl, heterocycle, ring,*

linking group, aminoacid residue, etc", derivatives thereof extend (irrealistically) the scope of the claims beyond what has actually been verified in the worked examples on file.

Furthermore, a term like *isomers* includes not only geometrical or optical isomers but also positional isomers comprising any possible structure which can be associated to the inventive molecules (for instance, pharmacophoric or biophoric rests). It is not apparent from the application which structural features must be necessarily present, neither any indication as to what falls within this definition.

Undefined terms render the claims **obscure in scope** and do not allow to correctly and specifically circumscribe a scope where the invention applies and for which protection can actually be granted.

The question is whether or not a technical effect is to be achieved by all the embodiments covered by the claims when this technical effect turns out to be the sole reason for the alleged inventiveness of these processes. A consequence is that broad expressions are objectionable under Art. 33(3) PCT.

A legal principle is that the extent of a patent monopoly is justified by the technical contribution to the art. This principle which is applied in relation to the extent of the protection that is justified by reference to Art. 5 and 6 PCT also governs the decision which is required to be made under Art. 33(3) PCT, for everything falling within a valid claim has to be inventive. Judgement of inventive step depends on whether the specific technical purpose (a surprising or unexpected correlation between a structure and an activity) can be credibly achieved over the whole range claimed. A second legal principle is that any one who alleges a fact has the onus of proving this allegation by appropriate evidence. The fact that test results show that ***some*** of the claimed compounds are indeed active cannot be regarded as sufficient evidence to lead to the inference that substantially ***all*** the claimed compounds possess this activity. The burden of proof that all the compounds claimed possess the alleged activity rests only upon the shoulders of the person alleging it.

3.4.2 The (given) examples (and particularly the tested ones) represent a relatively narrow illustration of the claimed scope (they have been already taken as a basis for the limitation of the search scope presently examined). It can be therefore questioned whether

the regularly occuring groups in the examples form a necessary and essential characterisitic of the invention which should not be allowed to vary out of the ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants, (especially keeping in mind that the difference with the prior art is relatively small, the effect (to be unexpected for an inventive step recognition) of which can be hindered by other unpredicted effects of larger structural variations of other variant groups that a skilled person cannot consider as obvious equivalents). Without any evidence of the contrary, the claimed scope do not represent a reasonable generalization of the very invention as shown by the examples.

Generalisations of concrete examples appear to be acceptable if they are not contradictory to the basis of qualitative or quantitative structure-activity-relationships (SAR) which says that for compounds with a certain chemical basic structure the known biological activity can *prima facie* be expected to be retained when making small structural modifications. These principles are well known to skilled persons in pharmacology and drug design and, if such principle would no longer apply at all, no generic formula in claims would be allowable at all for a pharmaceutical patent which then logically would have to be restricted to the concretely tested example(s).
It appears to be contradictory, on one hand to argue that, thanks to a very small structural modification on a position in a molecule, the known biological activity is surprisingly maintained or improved and, on the other hand, to claim a large number of structurally very different families of substituents through the above disputed terms (and their combinations) at various positions of the molecule under consideration.

Reasonable predictions of relations between chemical structures and biological activities are in principle possible, but **there is a limit** beyond which no such prediction can be validly made. It is therefore necessary to fix limits to the claimed scope.

3.4.3 Open and too broad formulations may also lead to unacceptable **speculations** from the skilled people as to the very invention and its future aspects; it may even suggest that the claimed scope lacks any inventive merit and is not properly covered by the description and, particularly, the examples. Furthermore this would deprive any third party from a legitimate protection for a genuine invention in relation with an object which was neither described nor even foreseen but would have only been a hypothesis in the frame of the present invention.

When only some and not substantially all claimed compounds exhibit a particular technical effect, the conclusion has to be that the invention as broadly defined in the independent claim was not a solution to the technical problem of achieving the given technical effect (with the consequence that the alleged technical effect of some of the claimed compounds is to be disregarded when determining the objective problem underlying the invention and thus when assessing inventive step). In other words, a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds. A general formulation, made up of many variables or groups defined by unlimited and/or vagues terms or non limitative expressions (including unspecific points of attachement), constitutes an excessive generalization encompassing forms which go far beyond what the skilled person, also taking into account physico-chemical and biological considerations, can regard as including obvious modifications, equivalents and/or (bio)isosterical values of substituents/of the examples given in the description.

There is indeed a great variety of structural possibilities which are claimed (and not yet explored by the Applicant), the *effect of which cannot be foreseen* having regard to the problem underlying the present application and, consequently, which are not solutions of the problem.

3.4.4 The inventive step required by Art. 33(3) PCT can be acknowledged only for a well-defined scope embracing a specific domain thanks to a reasonable generalisation of the very invention, taking into account the extent of the illustration of the examples, the support of the specification, the closeness of the prior art, the reproducibility and the feasability of the invention. In other words, the protected scope should comprise only compounds, their variants and equivalents which solve the problem underlying the invention, (what is a prerequisite for the acknowledgement of an inventive step).

As chemical species can be precisely defined by the identity and the number of the atoms involved, it is necessary to specify the disputed expressions and terms by means of the incorporation of the definitions given in the specification.

4. Miscellaneous

4.1 Since examples are, by definition, illustrative of the invention, they normally should not serve any limiting purpose. Any expression like "by way of example and not limitation, etc" (cf. page 75) should be avoided.

Any expression or sentence which may also refer to an extent of protection beyond the actual invention is also objectionable. The insertion of such sentences and/or part of sentences would suggest that the subject-matter as presently disclosed does not cover properly the claimed scope. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself. A precautionary measure on the limits of the scope is therefore superfluous and even misleading as it finally prevents a proper definition of the invention and opens the way to speculations (of skilled persons) about the very inventive subject-matter. Consequently any element against clarity has to be deleted.

In this sense, the expression "incorporated expressly herein by reference" is irrelevant and should be deleted.

4.2 It is additionally noted that the terms and/or expressions such as "etc", "and the like" are unspecific. They cannot serve as a support for the invention and therefore should be deleted. Note that parts of the description which are obviously not related to the claimed subject-matter like definitions of groups which are not even mentioned in the claims should also be deleted.

4.3 References to methods of treatment or diagnostic methods as "embodiments" of the invention must be avoided since they are considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT. The description can be redrafted in order to fulfil the PCT requirements.

4.4 The reference to WO 00204425 in the descriptionn is erroneous and should read WO 0204425. It appears that claim 69 merely repeats claim 66.

4.5 The reference to WO 2004/05286 in claim 77 is considered to lead a lack of clarity.

Re Item VI

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2005063744	14.07.2055	21.12.2004	22.12.2003 02.01.2004 26.07.2004

Re Item VII

To meet the requirements of Rule 5.1(a) PCT, cited prior art documents should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/015553	06.07.2007	07.07.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/14 A61K31/4353 A61P31/12

Applicant
GILEAD SCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	BOURGHIDA, E Telephone No. +31 70 340-9517

Form (PCT/ISA/237) (Cover Sheet) (April 2005)